ORIGINAL RESEARCH

Comparing Ketamine and Dexmedetomidine for Reducing Surgical Stress and Managing Postoperative Pain: A Retrospective Study

[1]Dr. Rajeev Babu, [2]Dr. Krishna Kumar

[1]Senior Resident, Department of Anaesthesia, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India
[2]Assistant Professor, Head of Department, Department of Anaesthesia, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India

Corresponding Author: Dr. Rajeev Babu
Senior Resident, Department of Anaesthesia, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India
Email:rajeev_drbabu@yahoo.co.in

Received: 17 November, 2018 Accepted: 21 December, 2018 Published: 10 January, 2019

ABSTRACT
Background: Bodies exhibit a stress response due to surgical procedures. This response includes endocrine, metabolic, hematologic, and immunologic reactions. The present study was conducted to compare ketamine and dexmedetomidine sedation in the attenuation of surgical stress response and postoperative pain.
Materials & Methods:74 cases of inguinal hernia of both genders were divided into 2 groups of 37 each. Intravenous ketamine was given at a dosage of 0.2-0.3 mg/kg in group I, while in group II, an infusion of dexmedetomidine at 0.4-0.5 mg/kg/hour was initiated. The following data were recorded: operation time, sedation drug, preoperative CRP and leukocyte levels, CRP and leukocyte levels at the 24th postoperative hour, and Visual Analogue Scale (VAS) score at the 24th postoperative hour.
Results: In group I and II, age was 48.2±1.4 years and 46.1±3.5 years, sex (female/male) ratio found to be 20:17 and 18:19, operation time (minutes) was 51.4 and 53.2, preoperative leukocyte (10^3/µL) was 6.4 and 6.9 and preoperative CRP (mg/L) was 3.2 and 3.7 respectively. The difference was non- significant (P> 0.05). The mean postoperative leukocyte (10^3/µL) count was 41.6±4.5 and 64.3±2.9, postoperative CRP (mg/dL) was 13.5±2.3 and 13.2±2.5 and postoperative 24th hour VAS was 2.1±1.6 and 3.2±1.1 in group I and II respectively. The difference was non- significant (P> 0.05).
Conclusion: It was found that ketamine sedation is more effective than dexmedetomidine sedation in reducing the surgical stress response. It was found that serum CRP, an acute-phase protein measured postoperatively, correlated with pain scores following surgery.
Keywords: Ketamine, Dexmedetomidine, Operation time, Postoperative pain

INTRODUCTION

Bodies exhibit a stress response due to surgical procedures. This response includes endocrine, metabolic, hematologic, and immunologic reactions. By activating the hypothalamic-pituitary-adrenal axis, surgical stress leads to a rise in the secretion of endogenous catecholamines and glucocorticoids, as well as inflammatory mediators.[1] Interleukin-6 (IL-6), a proinflammatory cytokine, plays a key role in triggering the acute-phase response and is generated at the site of surgery. IL-1 and IL-6 release triggers liver synthesis of CRP. The rise in the CRP serum level is closely associated with the IL-6 level. Neutrophils play a role in the acute inflammatory response resulting from tissue trauma. For diapedesis, a greater quantity of neutrophils move through the vascular endothelium to reach the site of inflammation.[2]
It is well known that α-2 adrenoceptor agonists can reduce central sympathetic outflow and mitigate the surgical stress response. A very recent study has shown that when dexmedetomidine is used alongside Total

Intravenous Anaesthesia (TIVA), it reduces surgical stress responses while maintaining hemodynamic stability and resulting in minimal adverse effects during the operation. Another anaesthetic agent, dexmedetomidine, is known to lower inflammation and mortality by inhibiting cytokine secretion in both humans and animals.[3]

Dexmedetomidine, an a2 adrenoceptor agonist, has been used for sedative and analgesic purposes in intensive care units.[4]In recent years, its anti-inflammatory effects have been highlighted. Studies in animals and clinical trials in intensive care patients have shown that dexmedetomidine can reduce cytokine secretion, which subsequently alleviates inflammation and reduces mortality.[5]It was thought that excessive activation of the sympathetic nervous system and inflammation caused by cytokine secretion secondary to immune system interactions were alleviated by central sympatholytic effects of dexmedetomidine. This evidence suggests that harmful inflammatory responses can be suppressed by dexmedetomidine administration in patients who are stressed and have enhanced inflammatory reactions due to surgery and anaesthesia.[6]

AIM &OBJECTIVES

AThe present study was conducted to compare ketamine and dexmedetomidine sedation in the attenuation of surgical stress response and postoperative pain.

MATERIALS & METHODS

Study Design

This was a retrospective, comparative study evaluating the effects of ketamine versus dexmedetomidine sedation on the attenuation of surgical stress response and postoperative pain in patients undergoing unilateral inguinal hernia repair under spinal anaesthesia.

Study Population

A total of 74 patients of both genders who underwent elective unilateral inguinal hernia repair under spinal anaesthesia were included in the study. All patients had provided written informed consent to participate.

Study Place

The study was conducted in the Department of Anaesthesiology, Department of Anaesthesia, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India.

Study Duration: The data collection covered procedures performed over a 12-month period, from November 2017 to October 2018.

Ethical Considerations: The study was approved by the Institutional Ethics Committee. All patients included had given informed written consent for the use of their medical records for research purposes. Patient confidentiality was maintained throughout the study.

Inclusion Criteria

- Patients aged ≥18 years.
- Patients who underwent elective unilateral inguinal hernia repair under spinal anaesthesia.
- Patients who received either ketamine or dexmedetomidine as sedation.
- ASA physical status I or II.

Exclusion Criteria

- ASA physical status III or higher.
- Body Mass Index (BMI) >30 kg/m².
- History of chronic analgesic use or substance addiction.
- Administration of additional intraoperative analgesic agents apart from the standard protocol.

Study Procedure

All eligible patient records were retrieved from the hospital database. Demographic data (name, age, gender), operation time, and the type of sedation drug administered (ketamine or dexmedetomidine) were noted. All patients received spinal anaesthesia with a 27-gauge Quincke needle using 15 mg of 0.5% hyperbaric bupivacaine along with 20 μg of intrathecal fentanyl.

- **Group I (Ketamine Group):** Received intravenous ketamine at a dose of 0.2–0.3 mg/kg immediately after spinal anaesthesia.
- **Group II (Dexmedetomidine Group):** Received an intravenous infusion of dexmedetomidine at a rate of 0.4–0.5 μg/kg/hour after spinal anaesthesia.

Postoperative analgesia for all patients consisted of intravenous paracetamol 1000 mg every eight hours.

Surgical Technique

All patients underwent standardized unilateral open inguinal hernia repair performed by experienced surgeons. Surgical technique was uniform across both groups.

Investigations

The following parameters were retrieved from the patient files:

- **Preoperative investigations:** C-reactive protein (CRP) and leukocyte count.

- **Postoperative investigations:** CRP and leukocyte count at the 24th postoperative hour.
- **Pain assessment:** Visual Analogue Scale (VAS) score at the 24th postoperative hour.

Outcome Measures

Primary outcomes:

- Postoperative CRP and leukocyte levels (as markers of surgical stress).
- VAS score at the 24th postoperative hour (as a measure of postoperative pain).

Secondary outcomes:

- Operation time.
- Correlation between postoperative CRP level and VAS score.

Statistical Analysis

Data were analyzed using **SPSS version 20.0 (SPSS Inc., Chicago, IL)**. Descriptive statistics were presented as means, standard deviations, and percentages.

- **Normality testing:** Kolmogorov-Smirnov test.
- **Homogeneity of variance:**Levene's test.
- **Comparative tests:** Independent t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data.
- **Correlation analysis:** Pearson's correlation test was used to assess the relationship between VAS score and postoperative CRP levels.
- Chi-square test/ Fisher's exact test were used to compare categorical and continuous variables between groups.

A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and baseline characteristics of study participants

Parameters	Group I (n=37)	Group II (n=37)	P value
Mean Age (years)	48.2±1.4	46.1±3.5	0.21
Sex (female/male)	20:17	18:19	0.42
Operation time (minutes)	51.4±2.3	53.2±1.1	0.53
Preoperative leukocyte (10^3/µL)	6.4±1.7	6.9±1.9	0.92
Preoperative CRP (mg/L)	3.2±1.5	3.7±2.3	0.76

Table 1 shows that in group I and II, age was 48.2±1.4 years and 46.1±3.5 years, sex (female/male) ratio found to be 20:17 and 18:19, operation time (minutes) was 51.4 and 53.2, preoperative leukocyte (10^3/µL) was 6.4 and 6.9 and preoperative CRP (mg/L) was 3.2 and 3.7 respectively. The difference was non-significant (P> 0.05).

Table 2: Comparison of parameters between Group I (Ketamine) and Group II (Dexmedetomidine)

Parameters	Group I (Ketamine), n=37	Group II (Dexmedetomidine), n=37	P-value
Postoperative leukocyte (10^3/µL)	41.6 ± 4.5	64.3 ± 2.9	0.02
Postoperative CRP (mg/dL)	13.5 ± 2.3	13.2 ± 2.5	0.95
Postoperative 24th hour VAS	2.1 ± 1.6	3.2 ± 1.1	0.41

Table 2 and figure I show that the mean postoperative leukocyte count in Group I (Ketamine) was significantly lower (41.6 ± 4.5 × 10^3/µL) compared to Group II (Dexmedetomidine) (64.3 ± 2.9 × 10^3/µL). The p-value of 0.02 indicates a statistically significant difference, suggesting that ketamine may better attenuate the inflammatory response postoperatively. Postoperative C - reactive protein (CRP) levels were comparable between the two groups (13.5 ± 2.3 mg/dL in Group I vs. 13.2 ± 2.5 mg/dL in Group II). A p-value of 0.95 indicates no statistically significant difference, suggesting that both ketamine and dexmedetomidine had similar effects on CRP levels, a marker of acute inflammation.

The postoperative 24th-hour Visual Analogue Scale (VAS) score was lower in Group I (2.1 ± 1.6) compared to Group II (3.2 ± 1.1), indicating less perceived pain in the ketamine group.

However, the p-value of 0.41 indicates that this difference was not statistically significant.

Figure I: Comparison of postoperative leucocytes, CRP, and potoperative 24 th hour VAS

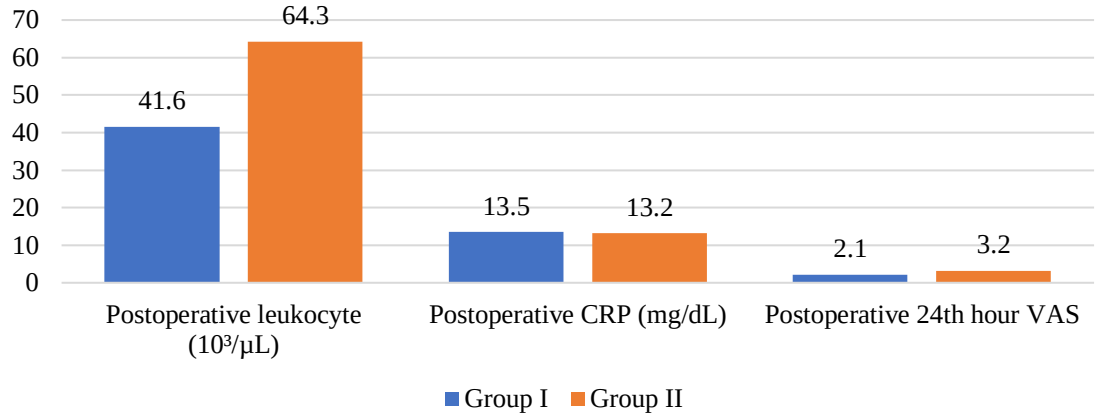

Table 3: Correlation between Postoperative CRP and VAS Score at 24 Hours

Variable 1	Variable 2	Test Used	r (Correlation Coefficient)	n	p-value
Postoperative CRP	Postoperative VAS	Spearman test	0.37	74	0.001

CRP: C-reactive protein, VAS: Visual Analog Scale, r: Correlation coefficient

Table 3 presents the results of a Spearman correlation test performed to assess the relationship between postoperative C-reactive protein (CRP) levels and the Visual Analogue Scale (VAS) pain scores at the 24th postoperative hour in a cohort of 74 patients undergoing unilateral inguinal hernia repair under spinal anaesthesia. The correlation coefficient (r = 0.37) indicates a moderate positive correlation between CRP levels and VAS scores. This suggests that as CRP levels increase, there is a tendency for postoperative pain scores to also increase. The p-value of 0.001 indicates that this correlation is statistically significant, meaning the observed relationship is unlikely due to chance.

DISCUSSION

Surgical stress response is believed to be a significant risk factor for unsatisfactory outcomes, especially in patients with cardiovascular, endocrine, metabolic and immune disorders.[7] Intraoperative modulation of stress response has been suggested to reduce postoperative complications and morbidity.[8] Therefore, perioperative inhibition of IL-6 and production of CRP from the liver have great importance.[9]

The present study was conducted to compare ketamine and dexmedetomidine sedation in the attenuation of surgical stress response and postoperative pain.

We found that in groups I and II, age was 48.2±1.4 years and 46.1±3.5 years; the sex (female/male) ratio was found to be 20:17 and 18:19; operation time (minutes) was 51.4 and 53.2; preoperative leukocyte (10³/µL) was 6.4 and 6.9; and preoperative CRP (mg/L) was 3.2 and 3.7, respectively. Kang SH et al.[10] in their study compared the effects of dexmedetomidine on inflammatory responses during and after surgery. Patients undergoing laparoscopic cholecystectomy were enrolled. After induction of anaesthesia, patients in the dexmedetomidine group (n = 24, group D) received a loading dose of dexmedetomidine (1.0 µg/kg), followed by infusion of dexmedetomidine at 0.5 µg/kg/h. A saline-treated group (n = 23, group S) served as a control. Intraoperative mean arterial pressure (MAP), heart rate (HR), and the amount of rescue analgesic administered as post-anaesthetic care were compared between the groups. The pro-inflammatory cytokines tumour necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, and anti-inflammatory cytokines IL-4 and IL-10 were quantified by sandwich enzyme-linked immunoassay at three times: after anaesthesia induction (T0), at the end of peritoneal closure

(T1), and 60 min after surgery (T2).The C-reactive protein (CRP) level and leukocyte count were measured on post-operative day 1. At time points T1 and T2, the IL-1β, TNF-α, and IL-10 levels were lower in group D than in group S ($P < 0.05$). The CRP level and leukocyte count on post-operative day 1 were also lower in group D ($P < 0.05$), as were intraoperative MAP, HR, and amount of rescue analgesic administered after surgery.

We observed that the mean postoperative leukocyte ($10^3/\mu L$) count was 41.6±4.5 and 64.3±2.9, postoperative CRP (mg/dL) was 13.5±2.3 and 13.2±2.5 and postoperative 24th hour VAS was 2.1±1.6 and 3.2±1.1 in group I and II respectively. The postoperative leukocyte count was significantly lower in the ketamine group compared to the dexmedetomidine group, suggesting a greater attenuation of the systemic inflammatory response. Ketamine is known for its immunomodulatory effects, particularly in suppressing pro-inflammatory cytokines such as IL-6 and TNF-α, and reducing neutrophil activation (Loix et al., 2011).[11] These effects likely contribute to the observed reduction in leukocyte counts postoperatively. Conversely, while dexmedetomidine also has anti-inflammatory properties through α2-adrenoceptor-mediated suppression of the sympathetic nervous system and cytokine release (Taniguchi et al., 2004), the effect may not be as profound in the early postoperative phase, as observed in this study.[12]

Postoperative CRP levels were not significantly different between the two groups, indicating that both ketamine and dexmedetomidine exerted a comparable effect on systemic inflammation as measured by CRP, a nonspecific acute-phase reactant. Although CRP is a reliable marker of inflammation, its peak typically occurs 24 to 48 hours postoperatively, and the lack of significant difference might be due to the timing of measurement or variability in individual inflammatory responses. Previous studies have shown mixed results, with some suggesting a reduction in CRP levels with dexmedetomidine due to decreased stress hormone release (Bekker A &Sturaitis M, 2005)., while others report similar anti-inflammatory efficacy with low-dose ketamine (Schwenk et al., 2018).[13,14]

VAS scores were lower in the ketamine group than in the dexmedetomidine group at 24 hours postoperatively, although the difference was not statistically significant. Ketamine, by acting as an NMDA receptor antagonist, disrupts central sensitization and has well-documented analgesic properties at sub-anesthetic doses (Subramaniam et al., 2004).[15]Dexmedetomidine, with its sedative and analgesic effects via α2-adrenergic receptor agonism, also provides effective postoperative pain control (Blaudszun et al., 2012).[16] The comparable VAS scores suggest that both agents are effective, though ketamine may offer a slight advantage in pain attenuation, especially in settings of heightened nociceptive input.

Altiparmaket al.[17] compared effects of ketamine, dexmedetomidine and determine correlation between postoperative pain scores and serum C-reactive protein on surgical stress response. Electronic records of 121 patients who had inguinal hernia repair were analysed retrospectively. Patients' age, sex, operation time, sedation drug, preoperative and postoperative C-Reactive Protein (CRP) and leukocyte levels, postoperative visual analogue scale scores were recorded. Postoperative mean CRP level was 42.3±9 mg/dL in ketamine group and 65.4±6.6 mg/dL in dexmedetomidine group. Mean visual analogue scale at postoperative 24th hour was 2.6±0.8 in ketamine group and 3±0.7 in dexmedetomidine level. These differences were statistically significant ($p<0.05$). Leukocyte counts were similar between groups. There was a moderate positive correlation between postoperative 24th hour CRP levels and pain scores.Senapathi TG et al.[17] determined the effectiveness of low-dose intravenous ketamine to attenuate stress response in patients undergoing emergency cesarean section with spinal anesthesia. Thirty-six pregnant women undergoing emergency cesarean section with spinal anesthesia were randomly divided into two groups (n=18). Ketamine 0.3 mg/kg (KET group) or NaCl 0.9% (NS group) was administered intravenously before the administration of spinal anesthesia. C-reactive protein (CRP) and neutrophil levels were measured preoperatively and postoperatively. Elevation of CRP stress response was lower in the KET group and significantly different ($P \leq 0.05$) from that in the NS group. Neutrophil level was elevated in both the groups and hence not significantly different from each other ($P > 0.05$). Postoperative visual analog scale pain score was not significantly different between the two groups ($P > 0.05$), but there was a statistically significant ($P \leq 0.05$) positive and weak correlation between visual analog scale and CRP level postoperatively.

CRP is an acute-phase reactant and a sensitive marker of systemic inflammation. Its levels typically rise in response to tissue injury and surgical stress. Previous studies have demonstrated that elevated postoperative CRP levels correlate with increased postoperative pain and delayed recovery. For instance, Kehlet and Dahl (2003) highlighted the role of inflammatory mediators, including CRP, in contributing to nociceptive sensitization and heightened pain perception in the immediate postoperative period.[18]Furthermore, the type of sedative agent used intraoperatively can influence the inflammatory response. In this study, patients sedated with ketamine showed a trend towards lower postoperative leukocyte counts and VAS scores, though only the leukocyte count difference was statistically significant. Ketamine's NMDA receptor antagonist properties may contribute to its analgesic and anti-inflammatory effects. According to Loix et al. (2011), ketamine suppresses pro-inflammatory cytokine production and may attenuate the acute phase response following surgery.[11]

LIMITATIONS OF THE STUDY

- Retrospective Design: As a retrospective study, the ability to control for all confounding variables was limited.
- Single-Centre Study: Conducted at one institution, which may affect the generalizability of the results.
- Limited Sample Size: The sample size of 74 may not be adequate for detecting small differences between the two groups.
- Lack of Long-Term Follow-Up: Only short-term postoperative parameters were evaluated; long-term outcomes such as chronic pain were not assessed.
- Lack of Randomization: Patients were not randomized to the sedation groups, introducing a risk of selection bias.
- Subjectivity in Pain Measurement: Although the VAS score is widely used, it remains a subjective measure of pain that could vary based on individual perception.

CONCLUSION

Author found that ketamine sedation is more effective than dexmedetomidine sedation in reducing the surgical stress response. Ketamine provided better attenuation of the postoperative inflammatory response, as evidenced by significantly lower leukocyte counts, while both ketamine and dexmedetomidine showed similar effects on CRP levels and postoperative pain. A moderate, significant correlation between CRP and VAS scores suggests an association between inflammation and pain intensity.

ACKNOWLEDGEMENT

The authors would like to express their sincere gratitude to the Department of Anaesthesiology, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, for their invaluable support in conducting this retrospective study. We are thankful to all the medical and nursing staff involved in the care of patients undergoing inguinal hernia repair, whose cooperation made the data collection possible.We also extend our appreciation to the Medical Records Department for assisting in retrieving patient data efficiently.We are deeply thankful to our guide Dr. Krishna Kumar, Head of Department, Assistant Professor, Department of Anaesthesia, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India, whose valuable insights, encouragement, and unwavering support have been instrumental throughout the course of this research.

REFERENCES

1. Brodner G, Van Aken H, Hertle L, Fobker M, Von Eckardstein A, Goeters C, et al. Multimodal perioperative management--combining thoracic epidural analgesia, forced mobilization, and oral nutrition--reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. Anesthesia and Analgesia. 2001;92(6):1594-600.
2. Wu X, Song X, Li N, Zhan L, Meng Q, Xia Z. Protective effects of dexmedetomidine on blunt chest trauma-induced pulmonary contusion in rats. The Journal of Trauma and Acute Care Surgery. 2013;74(2):524-30.
3. Peng M, Wang YL, Wang CY, Chen C. Dexmedetomidine attenuates lipopolysaccharide-induced proinflammatory response in primary microglia. The Journal of Surgical Research. 2013;179(1):e219-25.
4. Zilberstein G, Levy R, Rachinsky M, Fisher A, Greemberg L, Shapira Y, et al. Ketamine attenuates neutrophil activation after cardiopulmonary bypass. Anesthesia and analgesia. 2002;95(3):531-36.
5. Welters ID, Hafer G, Menzebach A, Muhling J, Neuhauser C, Browning P, et al. Ketamine inhibits transcription factors activator protein 1 and nuclear factorkappa B, interleukin-8 production, as well as CD11b and CD16 expression: studies in human leukocytes and

leukocytic cell lines. Anesthesia and Analgesia. 2010;110(3):934-41.
6. De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation. CNS neuroscience & therapeutics. 2013;19(6):403-10.
7. Lu HW, He GN, Ma H, Wang JK. Ketamine reduces inducible superoxide generation in human neutrophils in vitro by modulating the p38 mitogenactivated protein kinase (MAPK)-mediated pathway. Clinical and Experimental Immunology. 2010;160(3):450-56.
8. Bulow NM, Colpo E, Pereira RP, Correa EF, Waczuk EP, Duarte MF, et al. Dexmedetomidine decreases the inflammatory response to myocardial surgery under mini-cardiopulmonary bypass. Brazilian Journal of Medical and Biological Research. 2016;49(4):e4646.
9. Singh I, Sagare AP, Coma M, Perlmutter D, Gelein R, Bell RD, et al. Low levels of copper disrupt brain amyloid-beta homeostasis by altering its production and clearance. Proceedings of the National Academy of Sciences of the United States of America. 2013;110(36):14771-76.
10. Kang SH, Kim YS, Hong TH, Chae MS, Cho ML, Her YM, et al. Effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. ActaAnaesthesiologicaScandinavica. 2013; 57(4):480-87.
11. Loix, S., De Kock, M., &Henin, P. (2011). The anti-inflammatory effects of ketamine: state of the art. *ActaAnaesthesiologicaBelgica*, **62(1)**, 47–58.
12. Taniguchi, T., Kidani, Y., Kanakura, H., Takemoto, Y., & Yamamoto, K. (2004). Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. *Critical Care Medicine*, **32(6)**, 1322–1326.
13. Bekker, A., &Sturaitis, M. (2005).Dexmedetomidine for neurological surgery. *Neurosurgery*, 57(Suppl_1**)**, 1–10.
14. Schwenk, E. S., Viscusi, E. R., Buvanendran, A., et al. (2018). Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine. *Regional Anesthesia and Pain Medicine*, 43(5)**,** 456–466.
15. Subramaniam, K., Subramaniam, B., &Steinbrook, R. A. (2004). Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesthesia& Analgesia*, 99(2)**,** 482–495.
16. Blaudszun, G., Lysakowski, C., Elia, N., &Tramer, M. R. (2012). Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology*, 116(6)**,** 1312–1322.
17. Altiparmak B, ToKeR MK, Uysal AI. Ketamine versus dexmedetomidine sedation in the attenuation of surgical stress response and postoperative pain: A retrospective study. Journal of clinical and diagnostic research. 2018 Jun 1;12(6):UC10-2.
18. Senapathi TG, Widnyana IM, Wiryana M, Aribawa IG, Aryabiantara IW, Hartawan IG, et al. Effectiveness of low-dose intravenous ketamine to attenuate stress response in patients undergoing emergency cesarean section with spinal anesthesia. Journal of Pain Research. 2016;9:689-92.
19. Kehlet H, Dahl JB. *Anaesthesia, surgery, and challenges in postoperative recovery*. Lancet. 2003 Dec 6;362(9399):1921–1928.